Food and Drug Administration
Center for Drug Evaluation and Research

Advisory Committee for Reproductive Health Drugs

March 4, 2013

Errata to the FDA Briefing Materials for NDA 204-516, Paroxetine Mesylate for Vasomotor Symptoms

1. On page 13, the second sentence contained two errors:
In a study of 24 subjects taking paroxetine mesylate 7.5 mg once daily for 19 days, the steady-state maximum plasma concentration of paroxetine (Cmax) was 13.1 ng/mL and the total exposure (AUC) of paroxetine is eight times higher than that observed after a single dose.

The correct sentence should read:
In a study of 24 subjects taking paroxetine mesylate 7.5 mg once daily for 14 days, the steady-state maximum plasma concentration of paroxetine (Cmax) was 13.1 ng/mL and the total exposure ($AUC_{0\text{-}24\ hr}$) of paroxetine is ten times higher than that observed after a single dose.

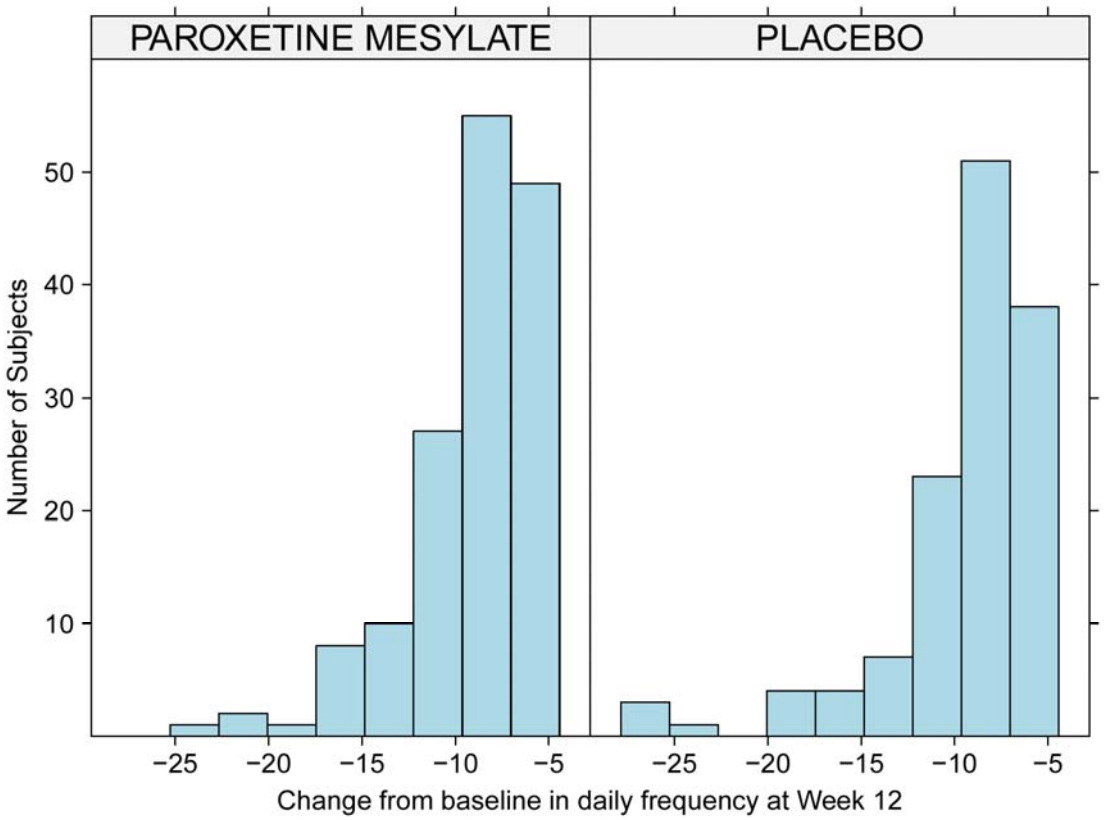
2. On page 16, Section 3.3.2, the primary endpoints were described as:
In both studies, the co-primary efficacy variables were:

- Mean change from baseline in average daily frequency of moderate to severe VMS at Week 4
- Mean change from baseline in average daily frequency of moderate to severe VMS at Week 12
- Mean change from baseline in average daily severity score of moderate to severe VMS Week 4
- Mean change from baseline in average daily severity score of moderate to severe VMS at Week 12

The correct statement should read:
In both studies, the co-primary efficacy variables were:

- Mean change from baseline in frequency of moderate to severe VMS per day at Week 4
- Mean change from baseline in frequency of moderate to severe VMS per day at Week 12
- Mean change from baseline in severity of moderate to severe VMS per day at Week 4
- Mean change from baseline in severity of moderate to severe VMS per day at Week 12

3. **Page 27, Figure 2: The data for Week 4 were inadvertently presented twice, rather than providing the data for Week 12 in the second figure. The correct figure for Week 12 is shown below:**



4. **Page 35, Table 13: The original tabulation counted some subjects in multiple cells. In addition, one paroxetine subject listed under "Met STS criteria for discontinuation" actually met these criteria at the baseline visit, but was inadvertently and briefly enrolled in the study. Therefore, her symptoms should not have been included as treatment-emergent.**

Table 13 Assessment of Suicidality

Criterion for Suicidality	Phase 1 Study 005 24 paroxetine	Phase 2 Study 002 49 paroxetine 52 placebo	Phase 3 Study 003 306 paroxetine 308 placebo	Phase 3 Study 004 285 paroxetine 285 placebo
Completed suicide	0	0	0	0
Suicide attempt	0	0	0	1 paroxetine 0 placebo
Treatment-emergent suicidal ideation, reported as AE/SAE	0	0	0	6 paroxetine 1 placebo
C-SSRS-reported suicidal behavior	0	NA	0	NA
C-SSRS-reported suicidal ideation	0	NA	0	NA
STS-reported suicidal behavior	NA	0 paroxetine 1 placebo	NA	6 paroxetine 4 placebo)
STS-reported suicidal ideation	NA	2 paroxetine 4 placebo	NA	27 paroxetine 29 placebo
Met C-SSRS criteria for discontinuation	0	NA	0*	NA
Met STS criteria for discontinuation	NA	0	0	3 paroxetine 1 placebo

*** Two subjects, one in each arm, met C-SSRS criteria for exclusion at baseline, but were inadvertently enrolled, then were discontinued shortly after starting study drug. They are not counted in this table, but are included in the safety population.**
NA = not applicable; instrument not used
Source: Clinical reviewer's tabulation

The corrected table below presents mutually exclusive cells (subjects are counted only once in the table):

Table 13 Assessment of Suicidality

Criterion for Suicidality	Phase 1 Study 005 24 paroxetine	Phase 2 Study 002 49 paroxetine 52 placebo	Phase 3 Study 003 306 paroxetine 308 placebo	Phase 3 Study 004 285 paroxetine 285 placebo
Completed suicide	0	0	0	0
Suicide attempt	0	0	0	1 paroxetine 0 placebo
Treatment-emergent suicidal ideation, reported as AE/SAE	0	0	0	4 paroxetine 0 placebo
C-SSRS-reported suicidal behavior	0	NA	0	NA
C-SSRS-reported suicidal ideation	0	NA	0	NA
STS-reported suicidal behavior	NA	0 paroxetine 1 placebo	NA	6 paroxetine 4 placebo
STS-reported suicidal ideation	NA	2 paroxetine 4 placebo	NA	21 paroxetine 28 placebo
Met C-SSRS criteria for discontinuation	0	NA	0*	NA
Met STS criteria for discontinuation	NA	0	0	1** paroxetine 1 placebo

***Two subjects, one in each arm, met C-SSRS criteria for exclusion at baseline, but were inadvertently enrolled, then were discontinued shortly after starting study drug. They are not counted in this table, but are included in the safety population.**
**** One paroxetine subject met STS criteria for exclusion at baseline, but was inadvertently enrolled, then discontinued shortly after starting study drug. She is not counted in this table, but is included in the safety population.**
NA = not applicable; instrument not used
Source: Clinical reviewer's tabulation

5. **Page 36, paragraph 3: the 56 events of STS-emergent suicidal ideation included seven subjects (six on paroxetine, one on placebo) whose events were also reported as SAEs or AEs. See corrected Table 13.**

6. **Page 37, Table 14: this table included three subjects who did <u>not</u> have their suicidality events reported as an SAE/AE. The original table is shown below:**

Table 14 Cases of Suicide Attempt/Ideation and Suicidal Ideation, Pooled Phase 3 Dataset

Study #/ Subject ID	Suicide Ideation/Attempt	Age (years) Race	Day of Onset	Reported AE/SAE	Drug/ Outcome
Suicide Attempt Resulting in an SAE					
N30-004/ 4-23-014	Suicide attempt with multiple non-study drug overdose; she reported suicidal thoughts; had past history of overusing prescription drugs & past mental health hospitalization, but had 0 scores on STS at baseline and early termination	50 Caucasian	54	**-SAE** -Suicide attempt	**Paroxetine** Discontinued
STS-Emergent Suicidal Ideation Resulting in an SAE					
N30-004/ 4-05-013*	STS-emergent suicidal ideation: indicated taking active steps to prepare for suicide attempt and intentional injury. When contacted, stated she thought about suicide "a little" but did not have specific plan. (Also met pre-specified STS discontinuation criteria: at baseline indicated wish to be dead)	61 Asian	166	**-SAE** -Suicidal ideation	**Paroxetine** Discontinued - Recovered without sequelae
N30-004/ 4-22-004	STS-emergent suicidal ideation: indicated wish to be dead, think about suicide, plan for suicide and taking active steps to prepare for suicide attempt	53 Caucasian	174	**-SAE** -Suicidal ideation -	**Paroxetine** Not discontinued - Recovered without sequelae
N30-004/ 4-23-023	STS-emergent suicidal ideation: indicated wish to be dead, and think about suicide. Subject also had dx of metastatic cancer.	67 Caucasian	168	**-SAE** -Suicidal ideation	**Paroxetine** Not discontinued– Recovered without sequelae
STS-Emergent Suicidal Ideation Resulting in an AE					
N30-004/ 4-48-022	STS-emergent suicidal ideation: indicated wish to be dead and think about suicide	50 African-American	83	**-AE** -Suicidal ideation	**Paroxetine** Discontinued
N30-004/ 4-45-017	Met pre-specified STS criteria for discontinuation: indicated wish to be dead, want to harm self and think about suicide	70 Caucasian	Took 2 doses	**-AE** -Suicidal ideation	**Paroxetine** Discontinued
N30-004/ 4-50-004	Met pre-specified STS criteria for discontinuation: indicated wish to be dead and want to harm self	66 Caucasian	83	**-AE** -Suicidal ideation	**Paroxetine** Discontinued
N30-004/ 4-73-026	Met pre-specified STS criteria for discontinuation: indicated wish to be dead and think about suicide	49 Caucasian	87	**-**No -Suicidal ideation	**Placebo** Discontinued

***Subject 4-05-013 was discontinued from the study due to an AE/SAE of suicidal ideation and also due to pre-specified discontinuation criteria based on STS score; therefore, the subject was counted as an AE and an SAE**
Source: SCS, Adapted from section on suicidality, page 63

See revised table below, which excludes these three subjects. Note that subject 4-45-017 met STS criteria for discontinuation at baseline but was inadvertently enrolled, then discontinued shortly after starting study drug.

Table 14 Cases of Suicide Attempt/Ideation and Suicidal Ideation, Pooled Phase 3 Dataset

Study #/ Subject ID	Suicide Ideation/Attempt	Age (years) Race	Day of Onset	Reported AE/SAE	Drug/ Outcome
Suicide Attempt Resulting in an SAE					
N30-004/ 4-23-014	Suicide attempt with multiple non-study drug overdose; she reported suicidal thoughts; had past history of overusing prescription drugs & past mental health hospitalization, but had 0 scores on STS at baseline and early termination	50 Caucasian	54	**-SAE** -Suicide attempt	**Paroxetine** Discontinued
STS-Emergent Suicidal Ideation Resulting in an SAE					
N30-004/ 4-05-013*	STS-emergent suicidal ideation: indicated taking active steps to prepare for suicide attempt and intentional injury. When contacted, stated she thought about suicide "a little" but did not have specific plan. (Also met pre-specified STS discontinuation criteria: at baseline indicated wish to be dead)	61 Asian	166	**-SAE** -Suicidal ideation	**Paroxetine** Discontinued - Recovered without sequelae
N30-004/ 4-22-004	STS-emergent suicidal ideation: indicated wish to be dead, think about suicide, plan for suicide and taking active steps to prepare for suicide attempt	53 Caucasian	174	**-SAE** -Suicidal ideation -	**Paroxetine** Not discontinued - Recovered without sequelae
N30-004/ 4-23-023	STS-emergent suicidal ideation: indicated wish to be dead, and think about suicide. Subject also had dx of metastatic cancer.	67 Caucasian	168	**-SAE** -Suicidal ideation	**Paroxetine** Not discontinued– Recovered without sequelae
STS-Emergent Suicidal Ideation Resulting in an AE					
N30-004/ 4-48-022	STS-emergent suicidal ideation: indicated wish to be dead and think about suicide	50 African-American	83	**-AE** -Suicidal ideation	**Paroxetine** Discontinued

***Subject 4-05-013 was discontinued from the study due to an AE/SAE of suicidal ideation and also due to pre-specified discontinuation criteria based on STS score; therefore, the subject was counted as an AE and an SAE**
Source: SCS, Adapted from section on suicidality, page 63

7. **Page 43, Table 20: The row for "subjects with suicidality" includes the following categories: Suicide attempt, treatment-emergent suicidal ideation, reported as an SAE/AE and Met STS criteria for discontinuation. One subject in the paroxetine arm who met STS criteria for discontinuation at baseline was mistakenly included in the original table.**

Table 20 Summary of AEs, Pooled Safety Dataset

Category	Paroxetine mesylate N=635[2] n (%)	Placebo N=641[3] n (%)
Subjects with any TEAE[1]	320 (50.4)	301 (47.0)
Deaths	1 (0.2)	0 (0)
Subjects with SAEs	14 (2.2)	9 (1.4)
Subjects with study drug discontinuations due to a TEAE	28 (4.4)	21 (3.3)
Subjects with suicidality	7 (1.1)	1 (0.2)
Subjects with a cardiovascular TEAE	27 (4.3)	17 (2.7)
Subjects with a hepatic TEAE	3 (0.5)	6 (0.9)
Subjects with gastrointestinal or bleeding TEAE	12 (1.9)	10 (1.6)

[1] TEAE: Any AE that started or worsened on or after the day of first dose
[2] A subject is counted only once within each category
Source: SCS, Page 43, Table 12

Revised Table:

Table 20 Summary of AEs, Pooled Safety Dataset

Category	Paroxetine mesylate N=635[2] n (%)	Placebo N=641[2] n (%)
Subjects with any TEAE[1]	320 (50.4)	301 (47.0)
Deaths	1 (0.2)	0 (0)
Subjects with SAEs	14 (2.2)	9 (1.4)
Subjects with study drug discontinuations due to a TEAE	28 (4.4)	21 (3.3)
Subjects with suicidality[3]	6 (0.9)	1 (0.2)
Subjects with a cardiovascular TEAE	27 (4.3)	17 (2.7)
Subjects with a hepatic TEAE	3 (0.5)	6 (0.9)
Subjects with gastrointestinal or bleeding TEAE	12 (1.9)	10 (1.6)

[1] TEAE: Any AE that started or worsened on or after the day of first dose
[2] A subject is counted only once within each category
[3] includes subjects in the following categories: "Suicide attempt," "treatment-emergent suicidal ideation, reported as an SAE/AE" and "Met STS criteria for discontinuation"
Source: SCS, Page 43, Table 12